EPA's Enhanced Reporting Program for Spot-on Products: An EPA Update

Presentation to
Chemical Specialty Producers Association
December 6, 2016
Marriot Harbor Beach Resort and Spa
Ft. Lauderdale, FL

David J. Miller CAPT|USPHS
Office of Pesticide Programs
U.S. Environmental Protection Agency

Overview

- Background on Spot-on products and 2010 EPA Analysis
- Spot-on Enhanced Quarterly Reporting Program, 2010+
- The development of Spot-on Incident Data Reporting Template
- Overview of Spot-on Pilot
- “What analyses will be done using the data?”
- Concluding Thoughts

Background on Spot-Ons

- In 2008-2009, an increase in the number of adverse reactions to pet spot-on flea and tick control products were reported to EPA's Incident Data System (IDS).
  - See https://www.epa.gov/pets/epa-evaluation-pet-spot-products-analysis-and-plans-reducing-harmful-effects
- In response, EPA formed an expert group which teamed with FDA-CVM and PMRA (Canada) to analyze the available data.
  - looked at both active and inert ingredients,
  - studied product labeling, and
  - discussed data needs for the future to improve analyses and regulation.
- On March 17, 2010, EPA announced the results of our analysis:
  - New Restrictions on Flea and Tick Products; Use Products with Extra Care
    - see also WSJ (3/18/2010): "**EPA to Require Beefed Up Labels for Pet Flea, Tick Products**"
  - Review of Enhanced Reporting of 2008 Pet Spot-on Incidents (EPA-HQ-OPP-2010-0229-0023)

Background on Spot-Ons

- EPA found that while most incidents were minor, pet deaths and "major incidents" have occurred.
- The products could be used safely but that some additional restrictions were needed
  - Label mitigation
  - Limitation of CSF to one formulation
  - 2 year time-limited registrations
  - Enhanced quarterly incident reporting
    - With sales data

Background on Spot-Ons

Additional findings/recommendations from 2010 review:

- **Standardized reporting** to be able to monitor these products better, and pursue more standardized reporting on adverse effects and sales.
  - Allow the Agency to more effectively review incidents, and if concerns are raised, give us information to act.
- **Pre-market clinical trials and post-market surveillance** to bring data requirements in line with FDA's requirements for similar products.
  - Increases consistency with how FDA regulates similar animal drugs, which includes pre-market clinical trials and a formal post-market surveillance program and will allow us to more thoroughly assess the safety of the products.
- For more information, see mitigation plan and slides (EPA-HQ-OPP-2010-0229-0024).

Enhanced Quarterly Spot-on Incident Reporting

- Appreciable efforts on the part of registrants to comply with enhanced reporting requirements
- The enhanced reporting data was compiled by HED during 2015 into electronic format for analysis
- Overall, the data was found to be inconsistent in format and terminology making the data difficult to analyze in a meaningful or useful way
  - Lack of standard terminology for adverse health events
  - Different data formats
    - PDFs, Excel, Word documents, etc.
  - Data collected had inconsistent structure
  - Missing important information
    - some data files had no EPA Registration Number
    - some records missing severity, outcome, etc.
    - no incident counts for some quarters or years
  - Sales data may be global for some companies, but U.S. only for other companies
    - Not necessarily consistent with incident counts
  - Reported total sales data included multiple products

The development of the Spot-on Incident Data Template

As result, little meaningful analysis possible

- To address this issue, EPA developed an Excel-based spot-on incident template for reporting spot-on incidents and sales
  - Seeks to standardize variables and definitions to permit meaningful analysis
  - Based on previous spot-on incident data submitted to EPA by spot-on registrants
    - Excel-based template for spot-on incident data reporting
    - Excel-based template for spot-on sales data reporting

The development of the Spot-on Incident Data Template

- EPA shared the spot-on template in early spring, 2016 and incorporated comments from the following sources:
  - Commercial Vendors/Service Providers
  - National Pesticide Information Center (NPIC)
  - Health Canada PMRA
- EPA met with FDA CVM on 18 April 2016
  - Shared the spot-on template and discussed with FDA CVM about their database systems and methodologies of data analysis
  - Incorporated their comments into the spot-on template

The development of the Spot-on Incident Data Template

- EPA decided to pilot the spreadsheet template/data submission program in mid-2016 and asked for up to 9 volunteer companies to participate for CY 2016.

Objective of Pilot

- Test the standard template that will facilitate submission and analysis of enhanced incident reporting
- Obtain feedback from pilot participants and other interested stakeholders regarding the feasibility and usability of the template to inform meaningful analyses of the data
- Use information from the pilot to modify the template based on registrant feedback and EPA experience

- EPA organized public webinar on 7 June 2016 to introduce proposed pilot program, ask for volunteers, and discuss planned statistical analysis
  - "Spot-on Incident Reporting Template & Statistical Analysis Plan"

Overview of EPA Spot-on Pilot Reporting Program

- Five registrants agreed in August 2016 to submit Spot On product incident data for 2016 Q1 and Q2 (January-June 2016) using the Excel-based data submission templates provided by EPA.
  - Provide feedback on the templates mid-year and post-Pilot
- Registrants submitted data in late August on several dozen spot-on products to the Agency using the EPA-provided Excel templates

What's Happened Since...

- EPA imported each pilot participant's Excel data into SAS
- EPA reviewed data and undertook data cleaning
  - Performed using custom SAS code, by company
  - NYT (8/17/2014): "For Big Data Scientists, 'Janitor Work' is Key Hurdle to Insights"
- EPA combined data from different pilot participants into one master (SAS) file and linked this with each company's product-specific sales data
- EPA undertook further data review (cross-tabulations, etc.) to look for outliers/unusual values, misinterpreted inputs/instructions, inconsistencies, missing values, etc.
- EPA converted the updated/corrected master SAS file into company-specific Excel file
- EPA provided pilot participant-specific data reviews and Excel data files to each company (separately) at the end of October
- EPA had (separate) follow-up conference calls/discussions with each pilot participant

EPA Overall Comments after review of Q1/Q2 pilot submissions

- EPA appreciates the registrants' willingness to participate in the pilot and work towards improving data submissions for better product stewardship
- Overall, the 5 participating spot-on registrants succeeded in following both the EPA sales and incident templates for their data submissions.
  - Notably, the pilot submissions demonstrated that providing largely useable and useful data in machine readable format for data analysis is possible
  - Important information included in the databases (body weight of animal, severity outcomes, symptoms, time of the incident, and sale volume/quarter, etc.
    - VedDRA terminology
  - But… there is room for improvement in consistency of format and clarity/interpretation of instructions
- Next submission for Q3 and Q4 expected in late February 2017

What analyses will be done using the data?

- **Level 0 :** Aggregate Query
  - Current OPP Incident Data System (IDS)
- **Level 1**: Reporting Odds Ratio, by Severity Outcome
  - evaluate the (Reporting) Odds Ratio of Death (or Death+Major) incidents of each product *vs*. all other products combined
- **Level 2**: Incident Rate Ratio, by Severity Outcome
  - Requires use of sales/dose data
- **Level 3**: Signal-Based Case-by-Case Review & Causality Analysis
  - Evaluate case by case basis, including narrative
    - IRR of symptoms
    - Causality analysis

NOTE: All example data are ficticious

What analyses will be done using the data?

Level 0: Review total (aggregate) incidents:

- IDS Aggregate query results – current method
  - IDS (Incident Data system) is maintained by OPP and incorporates data submitted by registrants under FIFRA section 6(a)(2), as well as other incidents reported directly to EPA
    - Domestic Animal (Pet) Incidents received from the Registrant are reported in aggregate form on a quarterly basis
      - This data includes the number of incidents reported for quarter, severity of the incidents, and products implicated
      - Does not include species or any narrative information regarding exposure scenario or symptoms

What analyses will be done using the data?

Level 0: Review total (aggregate) incidents:

- Summary can be done by product or by active ingredient
  - Which products have large number of incidents?
  - Below is an example table, by product (hypothetical data)

EPA Reg. No.	Death	Major	Moderate	Minor/UNK	Total
111111-12345*	200	700	1400	6050	8350
111111-67890	70	150	600	1500	2320
222222-00000	37	90	450	1102	1679

What analyses will be done using the data?

Level 0: Review total (aggregate) incidents:

- Summary can be done by product or active ingredient
  - Which products have large number of incidents?
  - Below is an example table, by product (hypothetical data)

EPA Reg. No.	Year	Death	Major	Moderate	Minor/UNK	Total
111111-12345*	2011	50	175	420	1813	2458
	2012	60	175	375	1215	1825
	2013	40	200	280	1362	1882
	2014	50	150	325	1660	2185
111111-67890	2012	13	50	250	350	663
	2013	25	45	125	325	520
	2014	18	65	225	340	648
222222-00000	2010	10	20	80	222	332

What analyses will be done using the data?

Level 1: Reporting Odds Ratio:

- Using incident database or IDS aggregate query results, we can calculate a Reporting Odds Ratio (ROR) for a given (severity) outcome
  - ROR used to compare odds of a given outcome (or event) for one product to odds of (same) outcome to another

What analyses will be done using the data?

Level 1: Reporting Odds Ratio:

- Using incident database or IDS aggregate query results, we can calculate a Reporting Odds Ratio (ROR) for a given (severity) outcome
  - ROR used to compare odds of a given outcome (or event) for one product to odds of (same) outcome to another

EPA Reg. No.	Product Name	Total cases	Deaths + Majors	ROR (95% C.I.)
111111-12345	**Product A**	**8350**	**900**	**1.27 (1.12, 1.45)**
111111-67890	**Product B**	**2320**	**220**	**0.92 (0.79, 1.07)**
222222-00000	**Product C**	**1679**	**127**	**0.70 (0.58, 0.84)**

"The odds of a death/major outcome (or event) for Product A are 1.27 times (95% CI: 1.12, 1.45) greater than the odds of a death/major outcome for "other than" Product A products"

What analyses will be done using the data?

Level 1: Reporting Odds Ratio:

Tree plots:

- describe the relative number of reported cases and the ROR among products
- Each rectangle in the figure represents a single product
- Area/size describes the total deaths + major + moderate cases of given product
- Color describes the relative ROR (deaths+majors+moderates) of a product
  - Red = ROR>2 (sign.)
  - Yellow = ROR>1 (sign.)
  - Green = N.S.

See **SUPPLEMENTAL ATTACHMENT** for details and additional information

Reference: Watson *et al.* (2005) The Toxic Exposure Surveillance System (TESS): Risk Assessment and Real-time Toxicovigilance across United States Poison Control Centers. *Toxicol. Appl. Pharmacol*, 207: S604-S610.

What analyses will be done using the data?

Level 2: Incident Rate Ratio:

- Combines Enhanced Incident Data with Sales Data
- **Incident Rate (IR)**: number of incidents per (e.g.) 10^6 doses sold or applied
- **Incident Rate Ratio (IRR)**: Ratio of two IRs
  - An IRR > 1 indicates the incident rate of the product is greater than the (blended or pooled) IR of all other products considered together

What analyses will be done using the data?

Level 2: Incident Rate Ratio:

- Combines Enhanced Incident Data with Sales Data
- **Incident Rate (IR)**: number of incidents per (e.g.) 10^6 doses sold or applied
- **Incident Rate Ratio (IRR)**: Ratio of two IRs
  - An IRR > 1 indicates the incident rate of the product is greater than the (blended or pooled) IR of all other products considered together

Outcome	Comparison	IRR (95% C.I.)
Death + major	**Product A vs. All other products (not A)***	**2.59 (2.29, 2.94)**
	Product B vs. All other products (not B)	**0.64 (0.56, 0.74)**
	Product C vs. All other products (not C)	**0.34 (0.28, 0.41)**

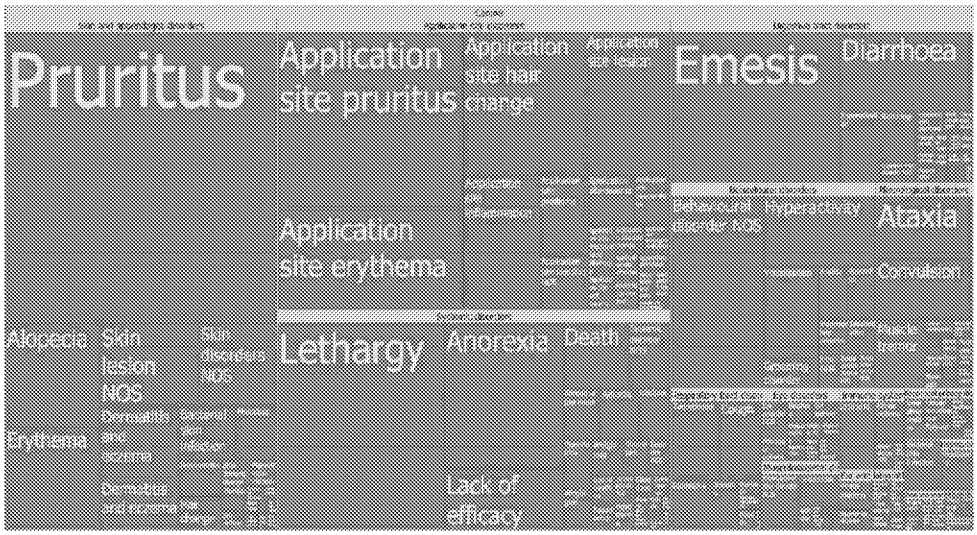
Assumes: (1) each product has 1 million doses in sales; (2) duration of use as per product label is: 2 months for product A(*) and 1 month each for products A and B.

What analyses will be done using the data?

Level 3: Signal-based case-by-case review

by specific symptom (e.g., VedDRA), by product

Tree Plot for **Product A:**

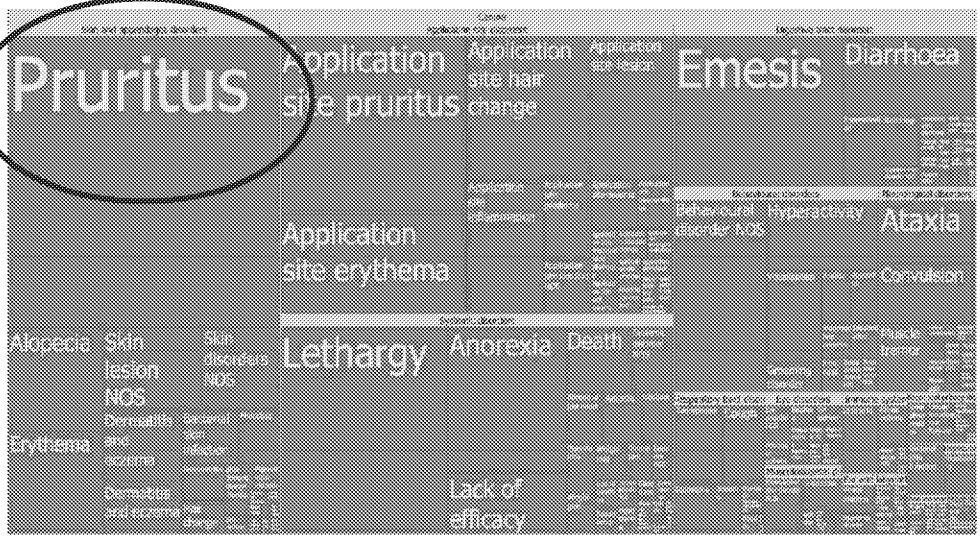


What analyses will be done using the data?

Level 3: Signal-based case-by-case review

by specific symptom (e.g., VedDRA), by product

Tree Plot for **Product A:**



What analyses will be done using the data?

Level 3: Signal-based case-by-case review

by specific symptom (e.g., VedDRA), by product

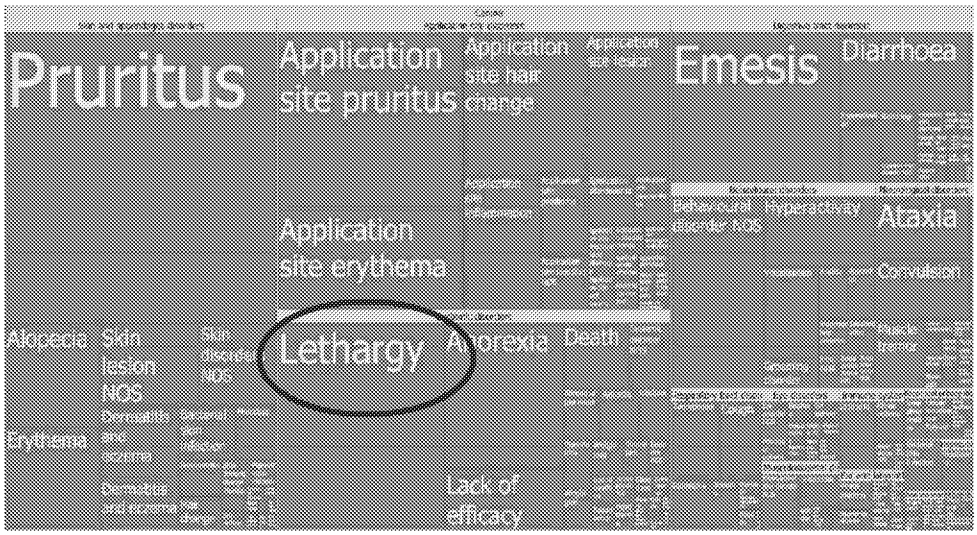
Outcome	Comparison	IRR (95% CI)
Pruritis	**Product A vs. All other products (not A)**	**1.14 (0.89, 1.24)**
	Product B vs. All other products (not B)	.45(0.36, 0.60)
	Product C vs. All other products (not C)	0.70 (0.10, 0.74)

What analyses will be done using the data?

Level 3: Signal-based case-by-case review

by specific symptom (e.g., VedDRA), by product

Tree Plot for **Product A:**



What analyses will be done using the data?

Level 3: Signal-based case-by-case review

by specific symptom (e.g., VedDRA), by product

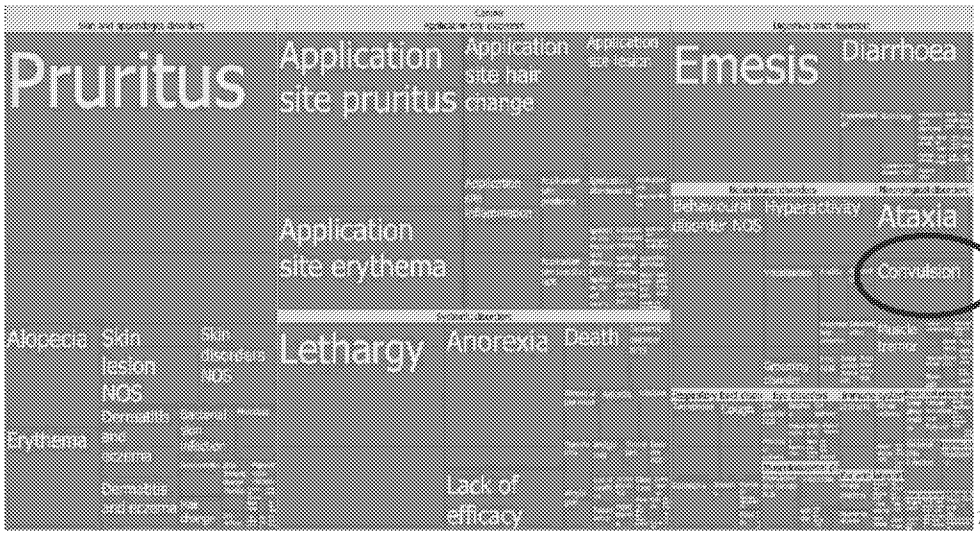
Outcome	Comparison	PRR (95% C.I)
Lethargy	**Product A vs. All other products (not A)**	**0.56 (0.43, 1.73)**
	Product B vs. All other products (not B)	1.32 (0.91, 1.76)
	Product C vs. All other products (not C)	[illegible]

What analyses will be done using the data?

Level 3: Signal-based case-by-case review

by specific symptom (e.g., VedDRA), by product

Tree Plot for **Product A:**



What analyses will be done using the data?

Level 3: Signal-based case-by-case review

by specific symptom (e.g., VedDRA), by product

Outcome	Comparison	[illegible]RR (95% C.I)
Convulsions	**Product A vs. All other products (not A)**	1.65 (1.48, 1.76)
	Product B vs. All other products (not B)	[illegible] (0.28, 0.7[illegible])
	Product C vs. All other products (not C)	0.21 (0.13, 0.56)

Caveats and Reminders:

- Signals are signals only –
  - Detected signals are hypotheses only, and do not imply causal relationships
  - Do not replace hands-on clinical review of case reports – medical judgement
  - "Disproportionalities" or SDR (signals of disproportionate reporting)
- Limitations and biases associated with reported data may limit utility
  - In any case, will require cautious interpretation
- Confidentiality
  - Analysis must be done such that a registrant will not be able to use results to derive the sales volume of any other specific registrants
    - In the IRR analysis, we will compare the incident rate of Product A to the incident rate of all other Products together

Concluding thoughts

- EPA recognizes that incident counts alone –as provided by EPA's IDS - may not be reliable for indicating concern
  - Need to consider "disproportionality"
- EPA has identified a need for standardized pet incident reporting and sales data reporting
  - Initiated a pilot program in which 5 spot-on registrants are participating
- Spot-on Pilot results for first 6 months have been submitted
  - so far – encouraging
- Importance of case-by-case review
  - Statistics are good for signal detection but are **not** a substitute for case-by-case analysis and narrative review
- Issue of confidential information
  - Analysis must be done such that a company will not be able to use results to derive the sales volume of any other specific companies

Concluding thoughts

- Timelines
  - Pilot – closing out December 2016
  - Next Steps - ?
  - Commercial PV Software
- Companies know their data and products best
- OPP – wide Incident Team & PPDC Incident Workgroup
- 6(a)(2) issues

Concluding thoughts

Good Product Stewardship

+

Appropriate Regulatory Oversight

=

Thank you.

Contact Information

For further questions, contact:

David J. Miller CAPT | US Public Health Service

Chief, Chemistry & Exposure Branch
and Acting Chief, Toxicology & Epidemiology Branch
Health Effects Division
Office of Pesticide Programs
email: Miller.DavidJ@epa.gov

Julie A. Breeden-Alemi, DVM

Registration Division
Office of Pesticide Programs
email: Breeden-Alemi.Julie@epa.gov

SUPPLEMENTAL ATTACHMENT

Data from: Watson, William A. *et al.* (2005) The Toxic Exposure Surveillance System (TESS): Risk Assessment and Real-time Toxicovigilance across United States Poison Control Centers. *Toxicol. Appl. Pharmacol*, 207: S604-S610.

- NOTE: The OR and associated C.I. on the next slide were **not** present in the original article but were instead calculated by EPA from the data provided.

Table 1
Hazard factor analysis and risk ratio for botanical products reported to TESS from 1993 through 2002

Product category	Cases with known outcomes	Hazard factor/ 1000 known outcomes	Rate ratio (95% CI)
Yohimbe	367	416.7	2.68 (1.59–2.80)
Ephedra (multi-ingredient)	10,690	207.1	1.33 (1.27–1.40)
Ephedra only	2604	250.0	1.25 (1.11–1.40)
Kava Kava	406	137.9	0.69 (0.48–0.97)
Valerian	464	112.1	0.56 (0.39–0.078)
Other multi-botanical products	1293	88.2	0.44 (0.35–0.054)
Ginseng	1140	83.3	0.42 (0.32–0.53)
Other single ingredient products	2363	82.1	0.41 (0.34–0.48)
Ginkgo biloba	568	74.5	0.37 (0.25–0.52)
St. John's Wort	910	65.9	0.33 (0.24–0.43)
Echinacea	892	47.2	0.24 (0.15–0.33)
Total	21,500	269.23	1.00 (0.96–1.04)

Hazard factor calculation: (moderate outcomes + major outcomes + deaths)/ number of cases with known outcomes (from Woolf et al., 2003).

See also: http://www.fda.gov/newsevents/testimony/ucm115044.htm
http://www.gao.gov/new.items/d031042t.pdf

SUPPLEMENTAL ATTACHMENT

Herbal	known cases	HF/1000	RR	A	B	C	D	**OR**	OR, LCB	OR, UCB
yohimbe	367	416.7	2.081107	153	214	4152	16981	2.92	2.37	3.61
ephedra-multi	10690	267.1	1.333966	2855	7835	1450	9360	2.35	2.19	2.52
epdedra only	2604	250	1.248564	651	1953	3654	15242	1.39	1.26	1.53
kava kava	406	137.9	0.688708	56	350	4249	16845	0.63	0.48	0.84
velerian	464	112.1	0.559856	52	412	4253	16783	0.50	0.37	0.67
other multi-botanical	1293	88.2	0.440493	114	1179	4191	16016	0.37	0.30	0.45
ginseng	1140	83.3	0.416022	95	1045	4210	16150	0.35	0.28	0.43
other single ingred.	2363	82.1	0.410028	194	2169	4111	15026	0.33	0.28	0.38
ginko biloba	564	74.5	0.372072	42	522	4263	16673	0.31	0.23	0.43
St. Johns Wort	910	65.9	0.329122	60	850	4245	16345	0.27	0.21	0.35
echinacia	699	47.2	0.235729	33	666	4272	16529	0.19	0.13	0.27

Data from: Watson, W.A. *et al.* (2005) The Toxic Exposure Surveillance System (TESS): Risk Assessment and Real-time Toxicovigilance across United States Poison Control Centers. *Toxicol. Appl. Pharmacol*, 207: S604-S610.
NOTE: The OR and associated C.I. were not present in the original article but were instead calculated by EPA from the data provided

TIMELINE FOR PILOT SPOT-ON PROGRAM

- **June 21, 2016**: deadline to express interest in participation
- **June 28, 2016**: selection of volunteers for pilot; participants will be notified
- **July 29, 2016**: Pilot companies submit 1st and 2nd quarter 2016 data using the template
- **Early August 2016**: follow-up webinar for volunteer pilot participants
  - Discussion of template usability and feasibility
- **November/December**: Individual pilot company follow-up & clarification of issues
- **February 28, 2017**: Pilot companies submit 3rd and 4th quarter data using refined template